Remarks

In the first paragraph of the Office Action, the Examiner refers to the prior restriction requirement and election, then states that:

> Claims 68-135 are pending. Claims 91 and 108-135 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention. Claims 68-90 and 92-107 are currently under consideration.

But in the response to the Restriction Requirement , filed on 3/25/2011, Applicants elected Group I (claims 68-107, 121-124 and 128). Accordingly, Applicants have included amendments to claims 121-124 and 128 as it appears these claims were elected and should still be pending.

The objections to claims 74 and 104 have been noted, and the claims have been amended, and these claims as now worded are grammatically correct and do not include spelling errors.

The rejection of claims 68, 75, 82 and 83 under Section 112, para. 2 has been overcome by amendments to claim 68 to include proper antecedent basis.

The Examiner rejected claims 68-90, 92, 93, and 97-107 under 35 U.S.C. 112, first paragraph, because: "the specification, while being enabling for methods wherein a particular microsatellite status of a colorectal cancer tumor is determined based on higher or lower levels of particular polynucleotides disclosed in Table 17 ...." is allegedly not enabling for the claims as previously worded. Claim 68 (from which all the claims in this rejection depend) has been amended to recite "wherein at least one of said gene expression products used to determine said hereditary or sporadic nature is selected from the group consisting of the genes listed in Table 13...." This is enabled because the specification, p 9, paragraph 2, states:

> In a preferred embodiment the prognostic marker is the hereditary or sporadic nature of the cancer. The hereditary or sporadic nature of the cancer can be determined through a number of steps comprising determining the presence and/or amount of gene expression products forming a pattern in the sample.

Page 27, lines 3-10 states:

> One embodiment relates to a method of determining the hereditary or sporadic nature of cancer as the prognostic marker in an individual having contracted cancer based on

> determination of the expression pattern of at least 2 genes, such as at least 3 genes, such as at least 4 genes, such as at least 5 genes, such as at least 6 genes, such as at least 7 genes, such as at least 8 genes, such as at least 9 genes, such as at least 10 genes selected from the group of genes listed in Table 13.

Also, in the examples, it notes (page 85, lines 15-20):

> In order to identify a gene set for identification of hereditary microsatellite instable tumors we applied 19 sporadic microsatellite instable samples and 18 microsatellite instable samples to supervised classification as described above. *We found ten genes we high scored for separation of sporadic MSI-H from hereditary MSI-H tumours* ***(Table 26).*** [emphasis added]

The Examiner is asked to note that Table 26 has the same ten genes listed as does Table 13. Accordingly, the genes in Table 13 have been definitively established as classifiers of sporadic vs. hereditary colon cancer, and the claims 68-90, 92, 93, and 97-107 are enabled.

The Examiner has also stated in connection with the lack of enablement rejection of claims 68-90, 92, 93, and 97-107, that:

> The specification teaches methods wherein a particular microsatellite status of a colorectal cancer tumor is determined based on higher or lower levels of particular polynucleotides disclosed in Table 17 and methods wherein downregulation of MLH1 polynucleotides in colorectal tumor samples is indicative of patients with sporadic disease and downregulation of PIWIL 1 polynucleotides in colorectal tumor samples is indicative of patients with hereditary cases (pages 67-69, in particular). Such teachings demonstrate that the method does not function as claimed because downregulation of PIWIL 1 polynucleotides in colorectal tumor samples is not indicative of patients with sporadic disease, as encompassed by the claims.

In amended claim 68, it recites: "determining, in a sample from the individual, the microsatellite status of the cancer and the hereditary or sporadic nature of said cancer from one or more patterns formed by the presence or amount of a plurality of gene expression products ...." The claim does not specify that certain genes are up-regulated or down-regulated in the pattern to determine the hereditary or sporadic nature of the cancer, and does not in any way rule out that down-regulation of PIWIL 1 is *not* indicative of sporadic disease.

The Examiner has also stated in connection with the lack of enablement rejection of claims 68-90, 92, 93, and 97-107, that: "It is further noted that evidence abounds in which protein levels do not correlate with alterations in mRNA levels. There are many steps in the pathway leading from DNA to protein, and

all of them can, in principle, be regulated." The recitation in amended claim 68 that "at least one of said gene expression products... is expressed by a gene in Table 13" overcomes this portion of the reasoning behind the rejection.

The Examiner rejected claim 94 under 35 U.S.C. 112, first paragraph. Claim 94, as amended, recites determining: "a pattern formed by the presence or amount of a plurality of gene expression products, said pattern being indicative of the microsatellite status of said colon cancer wherein at least one of said gene expression products is expressed by a gene in Table 17..." In Example 2, first paragraph, it notes the enabling experiments performed with the genes in Table 17:

> The performance of the classifier was tested using 1-5082 genes and found to be stable showing 2-5 errors when using 4 to several hundred genes (Fig. 2A). ***In the final classifier the 9 genes (Table 17) that were most frequently used in the crossvalidation were used*** which resulted in 3 errors (Fig. 2B).

The Examiner also notes the disclosure at pages 86-87 of the specification:

> Such teachings demonstrate that the method does not function as claimed because patients with Dukes' B tumors with microsatellite stable tumors do not exhibit *better* survival as compared to colorectal cancer patients with Dukes' B tumors with microsatellite instable tumors, as encompassed by the claims. It is further noted that the specification discloses microsatellite stability is not correlated with survival in patients with Dukes' C tumors receiving adjuvant chemotherapy.

Claim 94 is to "classifying the colon cancer based on the microsatellite status." It does not mention survival, which therefore should not be a consideration in assessing compliance with enablement.

The Examiner has rejected claims 95-96 under 35 U.S.C. 112, first paragraph, because:

> The specification, while being enabling for methods wherein downregulation of MLH1 polynucleotides in colorectal tumor samples is indicative of patients with sporadic disease and downregulation of PIWIL 1 polynucleotides in colorectal tumor samples is indicative of patients with hereditary cases ...[it] does not reasonably provide enablement for methods wherein just any classification of just any cancer is determined based on just any result....

Similar to the language in claim 68, independent claim 95 recites: "determining the hereditary or sporadic nature of the cancer in a sample from the individual by analyzing a pattern formed by the presence or amount of a plurality of gene expression products, said pattern being indicative of the hereditary or sporadic nature of said colon cancer wherein at least one of said gene expression products

is expressed by a gene in Table 13 ..." As noted above, page 85, lines 15-20 definitively establishes the genes in Table 13 (which are the same as in Table 26) as classifiers of sporadic vs. hereditary colon cancer. Regarding some of the Examiner's other comments, it is again noted that claims 95 and 96 do not specify that certain genes are up-regulated or down-regulated in the pattern to determine the hereditary or sporadic nature of the cancer, and these claims do not in any way rule out that down-regulation of PIWIL 1 is not indicative of sporadic disease. Furthermore, in response to other of the Examiner's comments, the claims do not encompass all gene expression products, but only those "expressed by a gene in Table 13...."

The Examiner rejected claims 69, 75, 82, 83, 95, 96, and 105 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner contends that: "the written description in this case only sets forth MLH1 polynucleotides and PIWIL 1 polynucleotides as gene expression products that form a pattern for sporadic or hereditary nature of colon cancer." As explained above, various statements and the examples fully support the claims, which recite that the expression of one or more genes from Table 13 form a pattern to identify the sporadic or hereditary nature of colon cancer. Accordingly, the rejection for lack of written description should be withdrawn. The Examiner has rejected claims 106-107 under 35 U.S.C. 112, first paragraph, because:

> The specification, while being enabling for a method of examining the sporadic or hereditary nature of colon cancer comprising detecting levels of MLH1 polynucleotides and PIWIL 1 polynucleotides in colorectal tumor samples wherein downregulation of MLH1 polynucleotides in colorectal tumor samples is indicative of patients with sporadic disease and downregulation of PIWIL 1 polynucleotides in colorectal tumor samples is indicative of patients with hereditary cases (pages 67-69, in particular), the specification does not reasonably provide enablement for methods of examining the sporadic or hereditary nature of colon cancer comprising performing just any histological examination of just any type of sample from a subject ....

Claims 106-107 depend from claim 68 and thus are to a determination using "gene expression products ... expressed by a gene in Table 13...." Analysis of these gene expression products in a histological examination, or by genotyping, is clearly enabled.

In conclusion, all rejections have been addressed and allowance is respectfully sought.

Respectfully Submitted,

/EPM/

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